CLAIMS

1.   A method of constructing a population of altered heavy chain variable region encoding nucleic acids, comprising:

a)   providing a representation of first and second reference amino acid sequences, said first reference sequence comprising the sequence of a donor heavy chain variable region, said donor variable region comprising

i) framework regions and ii) three complementarity-determining regions as defined by the combined definitions of Kabat and Chothia; said second reference sequence comprising the sequence of an acceptor heavy chain variable region comprising framework regions;

b)   synthesizing a) first oligonucleotides encoding portions of said framework regions of said acceptor heavy chain variable region, wherein said portions of said framework regions when compared to said second reference sequence are unmodified; and b) a population of second oligonucleotides, each encoding i) at least a portion of a first complementarity-determining region that has been modified, said first complementarity-determining region selected from the group consisting of HCDR1, HCDR2 and HCDR3, wherein said modified first complementarity-determining region comprises a different amino acid at one or more positions when compared to the corresponding donor complementarity determining regions of said first reference sequence and ii) one or more portions of unmodified framework regions which are capable of hybridizing to said first oligonucleotides;

c)   ' mixing said first oligonucleotides with said population of second oligonucleotides as to create overlapping oligonucleotides; and

d)   treating said overlapping oligonucleotides under conditions such that a population of altered heavy chain variable region encoding nucleic acids is constructed, wherein the framework regions encoded by said altered heavy chain variable region encoding nucleic acids are unmodified with respect to said second reference sequence.

2.   The method of Claim 1, wherein said representation of first and second reference sequences is in electronic form.

3.   The method of Claim 1, further comprising the step of (E) coexpressing said population of altered heavy chain variable region encoding nucleic acids with a light chain variable region encoding nucleic acid so as to produce a diverse population of altered heteromeric variable regions.

4.   The method of Claim 1, wherein said synthesizing comprises chemically synthesizing.

5.   The method of Claim 1, wherein said acceptor is human.

6.   The method of Claim 1, wherein said treating of step D) comprises extension by a polymerase.

7.   A method of constructing a population of altered light chain variable region encoding nucleic acids, comprising:

a)   providing a representation of first and second reference amino acid sequences, said first reference sequence comprising the sequence of a donor light chain variable region, said donor variable region comprising

i) framework regions and ii) three complementarity-determining regions as defined by the combined definitions of Kabat and Chothia; said second reference sequence comprising the sequence of an acceptor light chain variable region comprising framework regions;

b)   synthesizing a) first oligonucleotides encoding portions of said framework regions of said acceptor light chain variable region, wherein said portions of said framework regions when compared to said second reference sequence are unmodified; and b) a population of second oligonucleotides, each encoding i) at least a portion of a first complementarity-determining region that has been modified, said first complementarity-determining region selected from the group consisting of LCDR1, LCDR2 and LCDR3, wherein said modified first complementarity-determining region comprises a different amino acid at one or more positions when compared to the corresponding donor complementarity

determining regions of said first reference sequence and ii) one or more portions of unmodified framework regions which are capable of hybridizing to said first oligonucleotides;

c)   mixing said first oligonucleotides with said population of second oligonucleotides as to create overlapping oligonucleotides; and

5   d)   treating said overlapping oligonucleotides under conditions such that a population of altered light chain variable region encoding nucleic acids is constructed, wherein the framework regions encoded by said altered light chain variable region encoding nucleic acids are unmodified with respect to said second reference sequence.

8.   The method of Claim 7, wherein said representation of first and second

10   reference sequences is in electronic form.

9.   The method of Claim 7, further comprising the step of (E) coexpressing said population of altered light chain variable region encoding nucleic acids with a heavy chain variable region encoding nucleic acid so as to produce a diverse population of altered heteromeric variable regions.

15   10.   The method of Claim 7, wherein said synthesizing comprises chemically synthesizing.

11.   The method of Claim 7, wherein said acceptor is human.

12.   The method of Claim 7, wherein said treating of step D) comprises extension by a polymerase.

13.   A method of constructing a population of altered heavy chain variable region encoding nucleic acids, comprising:

A)   providing a representation of first and second reference amino acid sequences, said first reference sequence comprising the sequence of a donor heavy chain variable region, said donor variable region comprising i) framework regions and ii) three complementarity-determining regions as defined by the combined definitions of Kabat and Chothia; said second reference sequence comprising the sequence of an acceptor heavy chain variable region comprising framework regions;

B)   synthesizing a) a population of first oligonucleotides, each encoding at least a portion of a first complementarity-determining region selected from the group consisting of HCDR1, HCDR2 and HCDR3, wherein said modified first complementarity-determining region comprises a different amino acid at one or more positions when compared to the corresponding donor complementarity determining regions of said first reference sequence; and b) second oligonucleotides encoding i) portions of said framework regions of said acceptor heavy chain variable region, wherein said portions of said framework regions when compared to said reference sequence are unmodified and ii) one or more portions of a complementarity determining region which are capable of hybridizing to said population of first oligonucleotides;

C)   mixing said population of first oligonucleotides with said second oligonucleotides as to create overlapping oligonucleotides; and

D)   treating said overlapping oligonucleotides under conditions such that a population of altered heavy chain variable region encoding nucleic acids is constructed, wherein the framework regions encoded by said altered heavy chain variable region encoding nucleic acids are unmodified with respect to said second reference sequence.

14.   The method of Claim 13, wherein said representation of first and second reference sequences is in electronic form.

15.   The method of Claim 13, further comprising the step of (E) coexpressing said population of altered heavy chain variable region encoding nucleic acids with a light chain variable region encoding nucleic acid so as to produce a diverse population of altered heteromeric variable regions.

16.   The method of Claim 13, wherein said synthesizing comprises chemically synthesizing.

17.   The method of Claim 13, wherein said acceptor is human.

18.   The method of Claim 13, wherein said treating of step D) comprises extension by a polymerase.

19.   A method of constructing a population of altered light chain variable region encoding nucleic acids, comprising:

A)   providing a representation of first and second reference amino acid sequences, said first reference sequence comprising the sequence of a donor light chain variable region, said donor variable region comprising i) framework regions and ii) three complementarity-determining regions as defined by the combined definitions of Kabat and Chothia; said second reference sequence comprising the sequence of an acceptor light chain variable region comprising framework regions;

B)   synthesizing a) a population of first oligonucleotides, each encoding at least a portion of a first complementarity-determining region selected from the group consisting of LCDR1, LCDR2 and LCDR3, wherein said modified first complementarity-determining region comprises a different amino acid at one or more positions when compared to the corresponding donor complementarity determining regions of said first reference sequence; · and b) second oligonucleotides encoding i) portions of said framework regions of said acceptor light chain variable region, wherein said portions of said framework regions when compared to said reference sequence are unmodified and ii) one or more portions of a

complementarity determining region which are capable of hybridizing to said population of first oligonucleotides;

      C)   mixing said population of first oligonucleotides with said second oligonucleotides as to create overlapping oligonucleotides; and

      D)   treating said overlapping oligonucleotides under conditions such that a population of altered light chain variable region encoding nucleic acids is constructed, wherein the framework regions encoded by said altered light chain variable region encoding nucleic acids are unmodified with respect to said second reference sequence.

      20.   The method of Claim 19, wherein said representation of first and second reference sequences is in electronic form.

      21.   The method of Claim 19, further comprising the step of (E) coexpressing said population of altered light chain variable region encoding nucleic acids with a heavy chain variable region encoding nucleic acid so as to produce a diverse population of altered heteromeric variable regions.

      22.   The method of Claim 19, wherein said synthesizing comprises chemically synthesizing.

      23.   The method of Claim 19, wherein said acceptor is human.

      24.   The method of Claim 19, wherein said treating of step D) comprises extension by a polymerase.